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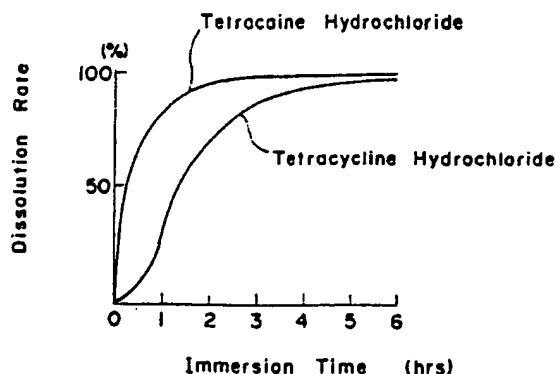
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54 Pharmaceutical composition for treating periodontal diseases.

57 A pharmaceutical composition for treating periodontal diseases which comprises one or more of therapeutically active ingredients dispersed in a carrier, characterized in that said carrier consists of

- (A) water soluble polymer, and
- (B) polymeric particles having a limited solubility in water, said particles being dispersed in said water soluble polymer.

Fig. 1



## PHARMACEUTICAL COMPOSITION FOR TREATING PERIODONTAL DISEASES

This invention relates to a pharmaceutical composition which is applied to a periodontal pocket or paradentium for the purpose of treating periodontal diseases. The pharmaceutical composition may be provided in the form of gel, sheet, film or bar-like formulation to release a controlled and effective amount of an active ingredient at the periodontal pocket or paradentium.

The "periodontal diseases" is a general term of various inflammatory diseases of paradentium. The diseases include a series of diseases exhibiting various syndromes which vary from each other according to the stage or situation of the diseases or the age of the patient, and have not been definitely subclassified. Since, however, the term "periodontal diseases" is given to any inflammatory disease which initially occurs at a marginal gingiva area and finally reaches an alveolar bone, the diseases can be roughly divided, on the basis of the degree of the inflammation, into "gingivitis" in which the inflammation is limited to the gingiva tissue, and "paradentitis" in which the inflammation is chronic and found even in an alveolar bone. However, peculiar diseases such as "juvenile paradentitis" and "acute necrotizing ulcerative gingivitis" are also included in the periodontal diseases.

The paradentitis, which was once called "alveolar pyorrhea", is characterized by remarkable symptoms such as inflammation of gingiva, formation periodontal pockets, bleeding and pus discharge from said periodontal pockets, and it brings about resorption of alveolar bone, loose tooth, and shedding of tooth.

The consensus of most investigators is that the periodontal diseases is caused by bacteria present in dental plaques formed in periodontal pockets. Efforts have been concentrated on the discovery of pathogenic bacteria responsible for said diseases. At the present time, an attributable major pathogen is recognized to be a certain nigral pigment-producing bacteria, such as genus Bacteroides. However, other genus of bacteria including Actinobacillus, Capnocytophaga, Fusobacterium and Spirochetes may be included in the causative pathogens. In any case, it is an established theory that the periodontal diseases should not be attributed to all bacteria present in the dental plaque.

The periodontal diseases has previously been treated by several ways, such as exhaustive scaling of plaques in periodontal pockets, root planing, gingivectomy to eliminate the periodontal pocket, or surgical curettage to excise inflammatory tissues. These treatments have been effective to some extent but not satisfactory.

On the other hand, pharmacotherapy has also been conducted using a drug selected from germicides, anti-inflammatory agents, plaque solubilizing agents, hemostyptics, and the like. These drugs are used in the form of the formulation suited for internal use or massotherapy (e.g., dentifrices, ointments, and the like). However, they are not satisfactory for the purpose of treatment of periodontal diseases because the internal use hardly permits the selective migration of the drug to the lesional region, and the massotherapy is not successful in solubilizing the plaques which are present beneath the gingival margin.

Recently, strips which comprise polymers and active ingredients for treatment of periodontal diseases have been developed. These strips are said useful for the treatment of plaques and inflammation beneath the gingival margin. The strips can be applied directly to the lesional region to be treated, and therefore, the active ingredient can be concentrated to the desired site selectively. This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy. For instance, J. M. Goodson et al. disclose the implantation of "hollow fiber", which contains germicides, into gingival resion (J. Clinical Periodontology, 1979: 6: 83-92). M. Addy et al. have reported the insertion of strips, which were prepared from a mixture of an insoluble polymer such as polyethylmethacrylate and germicides, into periodontal pockets (J. Periodontal, 693, Nov. 1982). In addition, insertion of the strips, prepared from a mixture of a soluble polymer and a drug, into the lesional region, such as periodontal pockets, is also reported (Japan Patent Publication No. 59-222406).

The formulations mentioned above comprise a mixture of an active ingredient and a homogeneous polymer base. Accordingly, where such formulation is designed to contain two or more active ingredients which differ each other in terms of pharmacological activity and therapeutically effective dose, it has been impossible to prepare the formulation in which each of the plural ingredients may release independently and provide its suitable concentration as desired.

The use of the hollow fiber or insoluble polymer, as a base, causes irritation or pain to patients, and moreover, it necessitates the removal of the base after release of an active ingredient, which is often annoying. On the other hand, the strip which comprises a soluble polymer as a base or carrier permits a rapid release of an active ingredient. Accordingly, it does not afford a constant therapeutic effect and, therefore, has a poor practical use.

As the result of an extensive study for seeking a novel therapeutical composition for periodontal diseases, which suitably controls the release of one or more of active ingredients and which does not give any uncomfortable feelings to patients, it has been found that the use of a two-phase carrier base, which consists of particles comprising a polymer having a limited solubility in water and a water soluble polymer used for dispersing such particles, meets the requirements just mentioned above.

Thus, the present invention provides a pharmaceutical composition for treating periodontal diseases, which comprises one or more of therapeutically active ingredients dispersed in a carrier, characterized in that said carrier consists of

- (A) water soluble polymer, and
- (B) polymeric particles having a limited solubility, said particles being dispersed in said water soluble polymer.

#### Brief Description of the Drawing

Fig. 1 shows the dissolution profile of two active ingredients contained in the pharmaceutical composition of the invention which is in the form of a film. Fig. 2 shows the dissolution profile of two active ingredients contained in a conventional composition.

The term "a polymer having a limited solubility in water" herein used includes an insoluble polymer, a sparingly soluble polymer, and a polymer which dissolves in an aqueous medium within a limited pH range.

For the purpose of the present invention, the term "insoluble polymer" means a polymer which dissolves in an aqueous medium, particularly in water, in a concentration of less than 0.1% by weight, irrespective of pH.

"Water soluble polymer" or "soluble polymer" denotes any polymer which dissolves in an aqueous medium, particularly in water, in a concentration of more than 1% by weight, irrespective of pH. "Sparingly soluble polymer" means a polymer which has a solubility between the soluble polymer and the insoluble polymer or decomposes to dissolve in vivo slowly. The term "polymer which dissolves in an aqueous medium within a limited pH range" means a polymer which dissolves in an aqueous medium, particularly in water, having a pH higher than 4 or lower than 6, in a concentration of more than 1% by weight.

For the purpose of simplicity, the insoluble polymer, sparingly soluble polymer and the polymer which dissolves in an aqueous medium within a limited pH range are hereinafter referred to as "non-soluble polymer" as a whole.

The soluble polymer used in the present invention must be fabricated into a semi-solid or a solid material. The non-soluble polymer should have a property suitable for being fabricated into particles. Both soluble and non-soluble polymers employed in the present application should be, of course, physiologically acceptable.

Specific examples of the insoluble polymer are ethyl cellulose, cellulose acetate, ethyl methacrylate / trimethylammonioethyl methacrylate chloride copolymer, and the like. The sparingly soluble polymer includes, for instance, biodegradable polymer such as polyglycolic acid, polylactic acid, polytetramethylglycolide, polydiethylglycolide, poly- $\epsilon$ -caprolactone, poly(DL-decalactone), poly(alkyleneadipate), copolymers thereof, and ion exchange resins.

The polymer which dissolves in an aqueous medium having a pH above 4 includes copolymers consisting of acrylic acid, methacrylic acid and/or esters thereof, such as methyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / octyl acrylate copolymer, ethyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / methyl methacrylate copolymer, and methyl methacrylate / methacrylic acid copolymer, hemiesters of organic bivalent acid with polysaccharide acetates such as cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, and amylose acetate phthalate, hemiesters of organic bivalent acid with alkylated polysaccharides such as methyl cellulose phthalate, hemiesters of organic bivalent acid with hydroxypropylmethyl cellulose phthalate, and hydroxyethyl ethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, alkyl ethers of carboxyalkylated polysaccharide such as carboxymethylcellulose, hemiesters of organic bivalent acid with polyvinyl alcohol and its derivatives such as polyvinyl alcohol phthalate, polyvinyl acetate phthalate, polyvinyl acetal phthalate, and polyvinyl butyrate phthalate.

The polymer which dissolves in an aqueous medium having a pH below 6 includes dimethylaminoethyl methacrylate / methyl methacrylate copolymer, polyvinylacetal / dimethylamino acetate, cellulose acetate dibutylhydroxypropyl ether, and the like.

Specific examples of the soluble polymer are, for instance, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pulluran, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and a salt thereof.

The pharmaceutical composition of the present invention may be prepared by dispersing one or more of active ingredients into a non-soluble polymer, or both of a soluble polymer and a non-soluble polymer, and mixing these polymers, and finally forming the resultant mixture into a solid material of a film, sheet or bar-like shape, or into a semi-solid material such as gel or ointment.

In more detail, one or more of non-soluble polymers is dissolved, as the first step, in an appropriate organic solvent. To the resultant solution is dissolved or dispersed one or more of active ingredients, and the mixture is formed into film or sheet by casting method. The resultant solid material is ground into particles.

The particles are also obtainable by spray drying, Wuster coating, Coacervation, or Drying in liquid phase. The average particle size may range from  $1\mu$  to  $500\mu$  depending on the contemplated release pattern of the active ingredient. However, the size between  $1\mu$  and  $300\mu$  is generally preferred.

On the other hand, one or more of water soluble polymers are dissolved in a suitable solvent. The solvent may contain, if desired, one or more of active ingredients. Subsequently, the pH of the mixture is adjusted, if necessary, and the particles obtained above are uniformly suspended in the mixture. The pharmaceutical composition of the invention in the form of gel is thus obtained.

The composition of the invention in the form of film or sheet is obtained by deaerating the just mentioned gel, and subjecting the same to the casting process. The film or sheet may also be prepared by compression molding, extrusion or calendering. The most suitable forming process among others is selected depending on the physico-chemical properties of the polymers employed.

The bar-like composition of the invention is prepared in the similar manner as the film or sheet, but through extrusion.

The weight ratio of the particles to the soluble polymer may range from 1:99 to 99:1 on the basis of dry weight. The composition of the particles: soluble polymer in a ratio of 10:90-70:30 is preferred.

Therapeutically active ingredient or ingredients used for the preparation of the composition of the invention are selected from those effective for prevention or treatment of periodontal diseases, for example, germicides, such as chlorhexidine, Ag protein, glyceryl iodide, phenol, benzalkonium chloride, cetylpyridinium chloride, and the like; antimicrobial agents, such as ampicillin, tetracycline, benzylpenicillin, clindamycin, cefalexin, erythromycin, chloramphenicol, fragiomycin sulfate, and the like; anti-inflammatory agents, such as

ibuprofen, indomethacin, ketoprofen, mefenamic acid, antipyrine, pranoprofen, ibufenac, tiaramide hydrochloride, prednisolon, dexamethasone, triamcinolone acetonide, prostaglandine, and the like; plaque solubilizing agents, such as dextranase, protease, amylase and the like; collagenase inhibitors obtained from the extraction of crude drugs, such as gambir-catechu known in the name of "asen'yaku"; local anesthetics, such as tetracaine hydrochloride, ethyl aminobenzoate, and the like; antihistaminic agents, such as chlorphenilamine maleate, diphenhydramine, and the like; hemostatic agents such as tranexamic acid, and the like.

The solid composition of the invention in the form of film, sheet or bar can be prepared in different sizes. However, the convenient size of the film or sheet may be 0.1-0.5 mm in thickness, 0.5-3 mm in width, and 10-50 mm in length. The size of the bar may generally range from 0.5 to 1.5 mm in diameter and from 10 to 50 mm in length. Furthermore, the composition of the invention may be cut in suitable size by the user depending on several factors, such as severity of the disease, and the width and depth of the locus to be applied. The composition of the invention can be applied to the periodontal pocket or paradentium by insertion, injection, or rubbing according to the type of formulation.

The pharmaceutical composition of the invention exhibits a desirably controlled release pattern of the active ingredient(s). Such controlled release is attained by careful selection of a particular condition with respect to the following variables.

(1) Distribution ratio of an active ingredient between the particles and the soluble polymer.

(2) The particle size to be dispersed in the soluble polymer.

(3) Selection of non-soluble polymer or polymers which permits the modification of both the solubility of particles and diffusion velocity of an active ingredient in the particles in the manner as desired.

(4) The use of one or more kind(s) of particles which differ from each other in their solubilities.

(5) The ratio of the amounts of particles and soluble polymer to be combined.

(6) Selection of soluble polymer or polymers having desired viscosity.

By selection of suitable conditions in regard to the above variables, there is obtained the pharmaceutical composition of the invention which releases one or more of active ingredients in the manner as contemplated. Since the surface of the composition of the invention is mainly composed of water soluble polymer, it does not give any uncomfortable feeling to patients.

The following examples are presented by way of illustration of specific embodiments of the pharmaceutical composition of the invention. In examples, part or parts are represented by weight basis.

#### Example 1

Poly(lactic acid) (10 parts) and tetracycline hydrochloride (2 parts) are dissolved in methylene chloride (100 parts). Flow casting of the resultant mixture yields a sheet, which is ground into particles having an average size of 50 $\mu$ .

The particles (10 parts) and hydroxypropyl cellulose (10 parts) are uniformly admixed. The mixture is blended with water, extruded with pressure, and dried. The bar-like shaped product of 1.0 mm diameter is thus obtained.

#### Example 2

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) is dissolved in ethanol (1000 parts). In the solution are suspended or dissolved indomethacin (5 parts) and triacetin (20 parts), and the mixture is casted into a sheet, which is then pulverized into particles having an average size of 80 $\mu$ .

Hydroxypropyl cellulose (10 parts) is dissolved in water (1000 parts), and tetracycline (25 parts) is added to the resultant solution, after adjusting to pH 6.0 by addition of hydrochloric acid. The resultant mixture (80 parts) are uniformly admixed with the particles obtained above (20 parts) to yield the product in a gel form.

#### Example 3

The particles produced in Example 2 (20 parts), methyl cellulose (80 parts) and tetracycline hydrochloride (5 parts) are uniformly admixed, and the resulting mixture is pressed to a sheet having a 500 $\mu$  thickness.

#### Experiment 1

The controlled release of an active ingredient was evaluated on the pharmaceutical composition of the invention which contains two kinds of active ingredients.

#### Method and materials

##### (1) Preparation of Sample

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) was dissolved in ethanol (1000 parts). Triacetin (20 parts) and tetracycline hydrochloride (8 parts) were then mixed with the resultant solution. The mixture was casted on a Teflon tray and dried at 40°C. The resultant sheet was pulverized into particles of 105 $\mu$  to 177 $\mu$  in size.

On the other hand, hydroxypropyl cellulose (viscosity of 2% aqueous solution is 1000 to 4000 cp at 20°C) (one part) was dissolved in water (99 parts). In the solution was dissolved tetracaine hydrochloride (0.03 part).

The hydroxypropyl cellulose solution and the particles are uniformly admixed at a weight ratio of 100:0.5, and the mixture is deaerated, casted on a Teflon tray with care to ensure the constant thickness, and air-dried to yield a film having 300 $\mu$  thickness.

In a solution of hydroxypropyl cellulose (1 part) dissolved in water (100 parts) were dissolved tetracycline hydrochloride (0.02 part) and tetracaine hydrochloride (0.02 parts), and the mixture was adjusted to pH 6, deaerated, casted on a Teflon tray, air-dried to obtain a film having 300 thickness, which was employed as a reference.

##### (2) Evaluation of Dissolution Rate

The dissolution rates of the active ingredients released from the films obtained above were measured using a phosphate buffer (500ml), pH 7.2, at 37°C, in accordance with the Rotating Basket Method (100 rpm) of Japanese Pharmacopoeia (X).

#### Results

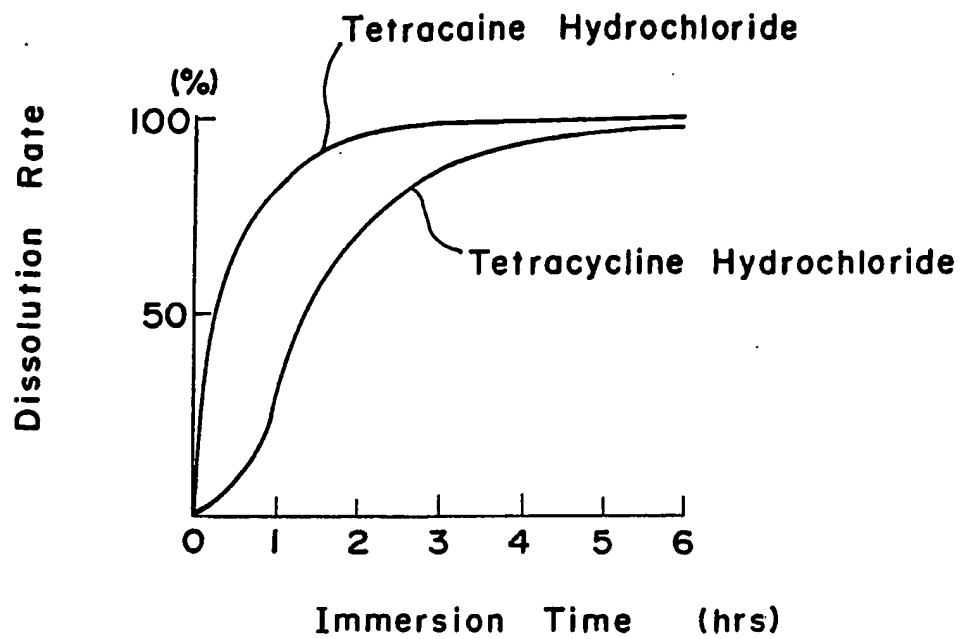
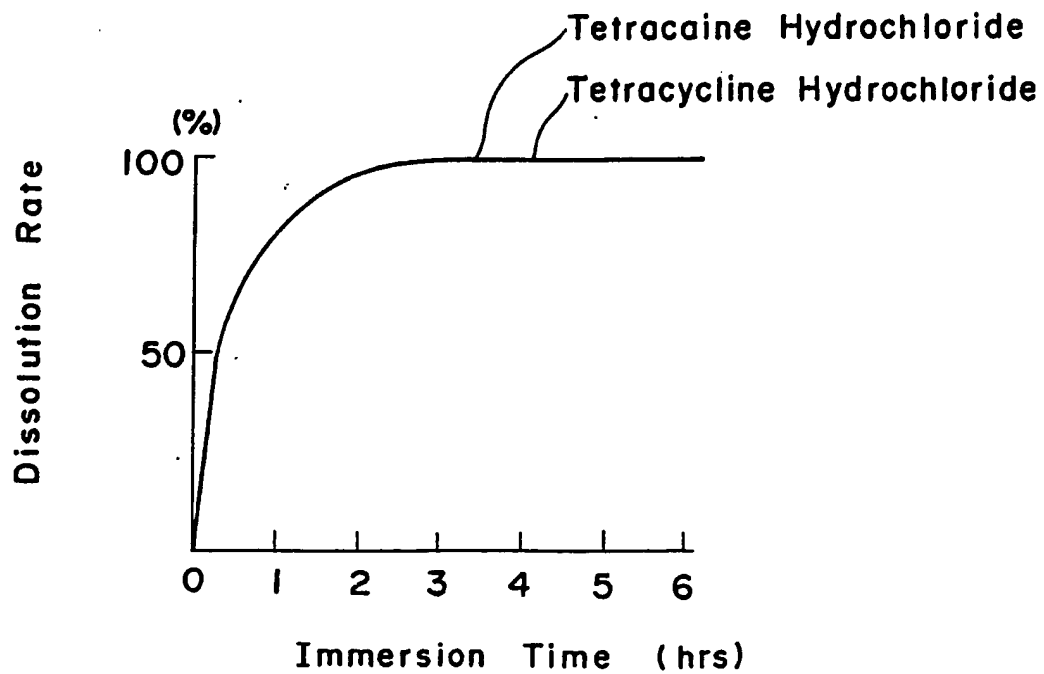
The dissolution profiles of the film of the invention and that of the reference are respectively shown in Fig. 1 and Fig. 2 of the accompanying drawing. The abscissa indicates immersion time and the ordinate indicates the dissolution rate. Fig. 1 shows that two active ingredients were released from the film with different release patterns while Fig. 2 shows the same and identical release pattern of the two active ingredients. Thus, this experiment illustrates that the composition of the invention permits separate control of the release patterns of two active ingredients. It also teaches that the composition of the invention in the form of a sustained

release formulation may be obtained where the same and identical active ingredient rather than the two active ingredients is employed in this experiment.

5. A pharmaceutical composition according to any preceding claim wherein said particles have an average size ranging from 1  $\mu\text{m}$  to 500  $\mu\text{m}$ .

## Claims

1. A pharmaceutical composition for treating periodontal diseases which comprises one or more of therapeutically active ingredients dispersed in a carrier, characterized in that said carrier consists of
  - (A) water soluble polymer, and
  - (B) polymeric particles having a limited solubility in water,
 said particles being dispersed in said water soluble polymer.
2. A pharmaceutical composition according to Claim 1 in the form of gel, sheet, film or bar.
3. A pharmaceutical composition according to Claim 1 or 2 wherein said particles are composed of one or more of compounds selected from ethyl cellulose, cellulose acetate, ethyl methacrylate / trimethylammonioethyl methacrylate chloride copolymer, ion-exchange resins, poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly- $\epsilon$ -caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / octylacrylate copolymer, ethyl acrylate / methacrylic acid copolymer, methyl acrylate / methacrylic acid / methylmethacrylate copolymer, methyl methacrylate / methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methyl methacrylate / dimethylaminoethyl methacrylate copolymer, polyvinylacetal / dimethylamino acetate, and cellulose acetate dibutylhydroxypropyl ether.
4. A pharmaceutical composition according to Claim 1, 2, or 3 wherein said water soluble polymer is selected from methyl cellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and a salt thereof.

**Fig. 1****Fig. 2**



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application number

EP 87 30 2514

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
P, X	EP-A-0 184 389 (SUNSTAR K.K. & LEDERLE (JAPAN) LTD.) * Page 4, lines 5-25; page 10, line 10 - page 11, line 8; page 12, lines 9-26 *	1-3	A 61 K 9/70 A 61 K 47/00
Y	DE-A-3 432 573 (THE KENDALL CO.) * Page 1, claim 1; page 9, line 1 - page 10, line 1; page 11, line 25 - page 13, line 32; page 14, line 28 - page 15, line 4; page 17, lines 4-21 *	1-4	
Y	US-A-4 568 535 (W.J. LOESCHE) * Column 1, lines 11-19; column 4, lines 57-69; column 7, lines 27-55 *	1-3	
Y	EP-A-0 135 022 (BEECHAM GROUP PLC) * Page 2, lines 5-28; page 3, lines 6-23; page 4, lines 1-21 *	4	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K A 61 L C 08 L
A	FR-A-2 148 045 (THE NATIONAL CASH REGISTER CO.) * Page 1, lines 1-7, 22-27, 35-39; page 2, line 9 - page 3, line 18; page 5, line 37 - page 6, line 10 *	1-3	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11-08-1987	Examiner MUELLNERS W.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	